

<b>Notice of Allowability</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/618,235	RUBINGH ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	William W. Moore	1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Applicant's communication filed 9 August 2004 and the interview conducted 17 August 2004.
2. ☒ The allowed claim(s) is/are 1-5 and 8-21.
3. ☐ The drawings filed on \_\_\_\_\_ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) ☐ All    b) ☐ Some\*    c) ☐ None    of the:
    1. ☐ Certified copies of the priority documents have been received.
    2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
  6. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
    - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date \_\_\_\_\_.
    - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

- |   |  |
|---|--|
| <ol style="list-style-type: none"> <li>1. <input type="checkbox"/> Notice of References Cited (PTO-892)</li> <li>2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</li> <li>3. <input type="checkbox"/> Information Disclosure Statements (PTO-1449 or PTO/SB/08),<br/>Paper No./Mail Date _____</li> <li>4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br/>of Biological Material</li> </ol> | <ol style="list-style-type: none"> <li>5. <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</li> <li>6. <input checked="" type="checkbox"/> Interview Summary (PTO-413),<br/>Paper No./Mail Date <u>20040817</u>.</li> <li>7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment</li> <li>8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance</li> <li>9. <input type="checkbox"/> Other _____.</li> </ol> |
|---|--|

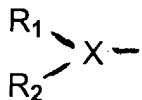
## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Cancel claims 6 and 7.

Rewrite claims 1-3, 8, 9, 12-15, and 19 thus:

1. (Amended) A protease conjugate comprising a microbial protease ~~moiety~~ and one or more addition moieties wherein the microbial protease ~~moiety~~ comprises a first epitope region, a second epitope region, and a third epitope region, wherein each addition moiety is covalently attached to an epitope protection position of the microbial protease ~~moiety~~, wherein:
  - (a) the epitope protection positions for the first epitope region are selected from the group of positions corresponding to positions consisting of 17 and 89 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1;
  - (b) the epitope protection positions for the second epitope region are selected from the group of positions corresponding to positions consisting of 52 and 134 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1; and,
  - (c) the epitope protection positions for the third epitope region are selected from the group of positions corresponding to positions consisting of 155 and 265 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1.
2. (Amended) A protease conjugate according to Claim 1 wherein each addition moiety, independently, has the structure:



wherein X is selected from the group consisting of a covalent bond ~~nil~~ and a linking moiety; R<sub>1</sub> is either absent or selected from the group consisting of ~~nil~~, a first

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polypeptide~~7~~ and a first polymer; R<sub>2</sub> is either absent or selected from the group consisting of ~~nil~~, a second polypeptide~~7~~ and a second polymer; and wherein at least one of X, R<sub>1</sub>, and R<sub>2</sub> is present ~~not nil~~.

3. (Amended) A protease conjugate according to Claim 2 wherein the microbial protease ~~moiety~~ has a modified amino acid sequence of a parent amino acid sequence, wherein the modified amino acid sequence comprises an amino acid ~~a substitution by a substituting amino acid~~ at one or more of the epitope protection positions and wherein each addition moiety is covalently attached to one of the substituting amino acids.
8. (Amended) A protease conjugate according to Claim ~~2~~ 6 wherein R<sub>2</sub> is absent ~~nil~~.
9. (Amended) A protease conjugate according to Claim ~~2~~ 6 wherein R<sub>1</sub> is absent ~~nil~~.
12. (Amended) A protease conjugate of claim 11 wherein the first polypeptide is covalently attached to the linking moiety or the protease ~~moiety~~ at a position of the first polypeptide selected from the group of positions corresponding to positions 1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 17, 22, 23, 24, 25, 26, 27, 36, 40, 41, 43, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 62, 63, 67, 86, 87, 89, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 143, 144, 145, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 206, 209, 210, 212, 213, 214, 215, 216, 253, 254, 256, 265, 267, 269, 271, 272, and 275 of the subtilisin BPN' amino acid sequence set forth in SEQ ID NO:1.
13. (Amended) A protease conjugate according to Claim 12 wherein X is a covalent bond which is a disulfide bond ~~nil attaching and wherein~~ the protease ~~moiety~~ and the first polypeptide ~~are covalently attached through a disulfide bond~~.

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14. (Amended) A protease conjugate according to Claim 6 wherein  $R_1$  is the first polymer and  $R_2$  is either absent or selected from the group consisting of nil and the second polymer.
15. (Amended) A protease conjugate according to Claim 14 wherein  $R_2$  is absent ~~nil~~ and the first polymer is polyethylene glycol.
19. (Amended) A protease conjugate according to Claim 1 wherein the addition moiety comprises ~~additionally comprising~~ one or more supplementary moieties selected from the group consisting of small molecules, polypeptides and polymers.

Authorization for this examiner's amendment was given in a telephone interview with Ms. Laura L. Frieko on August 17, 2004.

The following is an examiner's statement of reasons for allowance:

The above examiner's amendment cancels claims 6 and 7 because, while they had further limited the originally-filed claim 1, they cannot logically limit claim 5 that depends from the amended claim 1 where claim 6 states the very same six amino acid positions now recited by claim 1, and where claim 7 recites the very same two positions recited by that clause (a) of claim 6. The examiner's amendment accordingly amends claims 8 and 9 to depend from claim 2 rather than claim 6. The examiner's amendment further introduces a source limitation in claims 1 and 3, i.e., microbial, for the protease of the conjugate, a limitation that includes the prokaryotic and fungal proteases recited in claims 5 and 11. The examiner's amendment then clarifies intended embodiments of claims 2, 8, 9, and 13-15 by substituting the term "absent", with respect to structures of  $R_1$  and  $R_2$ , for the originally recited term "nil", because "nil" indicates the absence of a structure such as a polymer or polypeptide at a position  $R_1$  or  $R_2$  in claim 2. But with respect to the structure X in claim 2, "nil" is replaced with the phrase, "a covalent bond", because the claim cannot logically permit an absence of some sort of linking element lest no conjugate result, and because claim 13, which depends ultimately from claim 2,

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requires a covalent bond. The examiner's amendment conversely substitutes the phrase, "is present", for the term "not nil" in claim 2 because the claim must reasonably permit the presence of structures at one or more of X, R<sub>1</sub>, and R<sub>2</sub> in order that a conjugate exist. The examiner's amendment also simplifies, thus clarifies, recitations of claims 3 and 19 and amends claim 12 to provide a context for amino acid sequence positions claim 12 enumerates in accord with the recitation of claim 1 because claim 11 indicates that a "first polypeptide" of claims 11 and 12 is another microbial protease.

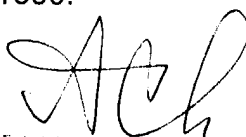
Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

#### *Conclusion*

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore  
August 17, 2004



WILLIAM W. MOORE  
Examiner  
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